Attention-specific effects of haloperidol on transient 40-Hz auditory response

J. Ahveninen[1,2,3], S. Kähkönen[1,2,4], H. Tiitinen[1,2], E. Pekkonen[1,2,3], J. Huttunen[2,3],
S. Kaakkola[3], R. J. Ilmoniemi[2], and I.P. Jääskeläinen[1,2]

[1]*Cognitive Brain Research Unit, Department of Psychology, P.O. Box 13, FIN-00014 University of Helsinki, Finland;* [2]*BioMag Laboratory, Medical Engineering Centre,* [3]*Department of Clinical Neurosciences, and* [4]*Department of Psychiatry, Helsinki University Central Hospital, FIN-00029 HUS, Finland*

1 Introduction

Selective attention refers to the ability to pick relevant stimuli embedded in a vast amount of information. Previous clinical and basic studies suggest that the dopamine system may be associated with this fundamental function [1,2], however, the exact neurochemical basis remains to be elucidated. The cerebral bases of selective attention, and other higher cognitive functions, have been associated with neural activity synchronized at around 40 Hz [3, 3]. For instance, the transient 40-Hz auditory response, detected with both electroencephalography (EEG) and magnetoencephalography (MEG) [5], is enhanced by selective attention [4] and gradually attenuated after long-term stimulation due to lessened vigilance [6]. Previous neuropharmacological studies, further, suggest that the transient 40-Hz response is attenuated by GABAA-agonist temazepine [7], and modulated by cholinergic muscarine receptors [8]. The dopaminergic modulation of transient 40-Hz auditory responses has not yet been investigated. Therefore, we studied the effects of the dopamine D_2-receptor antagonist haloperidol on the transient auditory 40-Hz response with a simultaneous 122-channel MEG and 64-channel EEG measurement.

2 Methods

Two milligrams of haloperidol or a matching placebo was administered orally to 11 right-handed healthy paid volunteers (aged 20-28 years; six females) in a double-blind, randomized crossover design, 3–4 hours before the recording. Based on the self reports, the subjects had no history of neurological or psychiatric disorders, previous exposition to neuroleptics, and they had used no drugs for 2 weeks, alcohol for at least 48 h, and caffeine and tobacco for 12 h before MEG and EEG recordings. The study was approved by the National Agency for Medicines, Finland, and Ethics Committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital. Written informed consent was obtained after the procedures had been fully explained to the subjects. All experimental sessions were carried out between 8 and 12 a.m., and the sessions were separated by one week.

During the recordings, the subject sat in a comfortable chair in a magnetically shielded room (Euroshield, Eura, Finland) with the head inside a helmet-shaped 122-channel whole-head MEG instrument [9] (Neuromag, Helsinki, Finland). The subjects were presented, dichotically through ear pieces and plastic tubes, with standard (700 Hz to the left ear, 1100 Hz to the right ear, $p = 0.44$ for each), and deviant (770 Hz to the left ear, and 1210 Hz to the right ear, $p = 0.06$ for each) 60-ms pure tones (with 5-ms rise and fall times) at 60 dB above the individually-determined subjective hearing threshold. The inter-stimulus interval (ISI) was random at 210–410 ms. The subjects were to attend to tones presented to one ear and to silently count the number of deviants, while ignoring tones presented to the other ear. The ear to be attended was counterbalanced across the subjects.

The magnetic 40-Hz response was measured with a 122-channel planar gradiometer and the simultaneous mastoid-referenced electric 40-Hz response with a 64-channel EEG using an electrode cap with 64 Ag/AgCl electrodes. Vertical and horizontal eye movements were recorded with an electro-oculogram (EOG). The recording pass-band was 0.03–100 Hz for EEG and MEG data and 0.5–30 Hz for the EOG (sampling rate 394 Hz for each). The analysis period was 800 ms (including a 100 ms pre-stimulus baseline). Epochs containing over 150 µV peak-to-peak changes in the EOG and EEG or over 3-pT/cm MEG changes, as well as the responses to the first few stimuli of the sequence, were automatically rejected. At least 500 artefact-free responses for the attended, and 500 for the unattended tones, were recorded, averaged and digitally band-pass filtered off-line at 32–48 Hz. The data were rectified before quantification.

Each two-channel MEG sensor unit measures two independent magnetic-field gradient components, $\partial B_z / \partial x$ and $\partial B_z / \partial y$, the z-axis being normal to the local helmet surface. The position of the subject's head relative to the MEG instrument was determined by measuring magnetic fields produced by 3 marker coils attached to the scalp. Before the measurement, the location of the marker coils in relation to cardinal points of the head (nasion, left, and right pre-auricular points) were determined using an Isotrak 3D-digitizer (Polhemus, Colchester, VT, USA).

The magnetic 40-Hz response amplitudes for both attended and unattended stimuli were quantified as the mean amplitude during the latency range of 30–130 ms from the channel pair showing the highest response amplitude over the left and right temporal areas ($|a| = [(\partial B_z/\partial x)^2 + (\partial B_z/\partial y)^2]^{1/2}$). Four MEG variables were calculated for each subject in each drug condition as follows: responses ipsilateral to the ear stimulated with attended or unattended stimuli and responses contralateral to the ear stimulated with attended or unattended stimuli. The dipole source of the gamma response was modeled using a spherical head model with a subset of 34 channels above each hemisphere. The dipole locations were fitted at consecutive peaks of the magnetic gamma oscillations at 30–130 ms post-stimulus.

The amplitudes of the electric 40-Hz response for both attended and unattended stimuli were quantified as the mean amplitude during the latency range of 30–130 ms analyzed using a signal-space projection (SSP) [10] calculated from signals obtained at 12 sites around frontal and vertex electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2, TP1, CPz, TP2). Because of insufficient signal-to-noise ratio (fewer summations), the electromagnetic signals elicited by the deviant tones were not analyzed. The EEG data of one subject was rejected because of excessive noise.

The effect of haloperidol on amplitude of the 40-Hz magnetic response over the contralateral and ipsilateral hemispheres to the attended ear was tested by a 4-way (attended ear by drug by attention by hemisphere) repeated measures ANOVA with contrasts. The effect of haloperidol on SSP of electric 40-Hz response was analyzed using a 3-way (attended ear by drug by attention) ANOVA with contrasts.

3 Results

In the placebo condition, the transient 40-Hz electric response was significantly enhanced by attention ($F(1, 8) = 13.2$, $p<0.01$). A significant drug main effect ($F(1, 8) = 6.6$, $p<0.05$) and a significant drug by attention interaction ($F(1, 8) = 13.8$, $p<0.01$) indicated that that the transient 40-Hz auditory electric response was attenuated by haloperidol (Table 1). The a priori contrasts, further, indicated that the attenuation by haloperidol was significant ($F(1, 8) = 21.8$, $p < 0.01$) for the 40-Hz electric response for the attended stimuli (Figure 1) but not for the unattended stimuli (Table 1). The differences in the amplitude of the transient 40-Hz magnetic response by haloperidol were, however, not statistically significant (Table 2).

Table 1. *Amplitudes of the 40-Hz electric response (μV).*

	Placebo		Haloperidol		
Stimuli	Mean	SD	Mean	SD	*p*
Attended	0.11	0.04	0.07	0.03	< 0.01
Unattended	0.09	0.03	0.08	0.02	N.S.

Table 2. *Amplitudes of the 40-Hz magnetic response (fT/cm) at the hemispheres ipsi- and contralateral to the ear stimulated.*

	Placebo		Haloperidol		
	Mean	SD	Mean	SD	*p*
Attended stimuli					
Contralateral	1.40	0.39	1.44	0.61	N.S.
Ipsilateral	1.49	0.39	1.52	0.28	N.S.
Unattended stimuli					
Contralateral	1.35	0.45	1.49	0.44	N.S.
Ipsilateral	1.25	0.29	1.33	0.63	N.S.

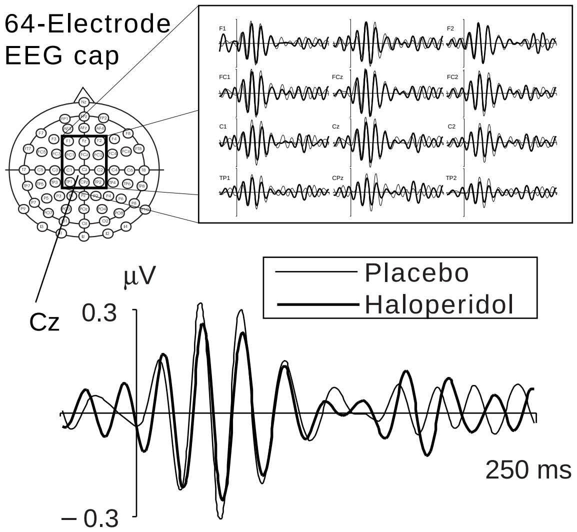

Figure 1. *Transient auditory-evoked electric 40-Hz auditory response elicited by the attended tones presented to the right ear in one subject.*

The dipole-source locations of the transient 40-Hz magnetic response were not affected by the drug or the level of attention. Supporting previous findings [5] the dipoles sources of transient 40-Hz magnetic responses were, on the average, located bilaterally 5 cm lateral to the sagittal and 1 cm anterior to the coronal (determined with left and right pre-auricular points) mid-line of the head.

4 Discussion

The dopamine D_2-receptor antagonist haloperidol significantly reduced the amplitude of the transient 40-Hz auditory electric response for the selectively attended tones, but no such effect was observed for the response to the unattended stimuli. During the placebo condition, the previously reported [4] enhancement of 40-Hz response by selective attention was clearly significant. The present results thus suggest that the blockage of dopamine D_2 receptors specifically abolish the attentional modulation of sources affecting the transient auditory gamma oscillations. It has been shown that haloperidol reduces glucose utilization in the frontal and anterior cingulate cortex [11], therefore, the attention-specific suppression of 40-Hz response may reflect haloperidol-induced hypoactivity in these brain regions that are known to be crucial for selective attention.

Despite the EEG results, no significant haloperidol effects were found in MEG. This discrepancy agrees with the theories [12] that the magnetic and electric aspects of gamma oscillations might be generated by at least partially distinct sources. At the same time the present haloperidol effects might have been mediated by radial sources (e.g. at the frontal brain regions), invisible to MEG but projecting to the fronto-central EEG leads, activated synchronously with the supratemporal sources [5] of the transient 40-Hz response. The absence of the dopamine D2-receptors from the human primary auditory cortex [13] might in turn account for lack of haloperidol effects on the tangential supratemporal sources of 40-Hz response that are detected by MEG. However, further studies on differences between magnetic and electric 40-Hz responses are clearly needed.

Acknowledgements

This work was supported by the Finnish Cultural Foundation, Helsinki University Central Hospital Research Funds, the Ella and Georg Ehrnrooth's Foundation, and the Academy of Finland. We thank Ms. Suvi Heikkilä and Mr. Teemu Peltonen for their assistance in carrying out the experiments.

References

1. J.T. Coull, "Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology", *Progr. Neurobiol.* **55,** 343-361, 1998.
2. P. Vieregge, R. Verleger, E. Wascher, F. Stuven and D. Kompf, "Auditory selective attention is impaired in Parkinson's disease--event-related evidence from EEG potentials", *Brain Res. Cogn. Brain Res.* **2,** 117-129, 1994.
3. A.K. Engel, P. König, A.K Kreiter, T.B. Schillen, and W. Singer, "Temporal coding in the visual cortex: new vistas on integration in the nervous system", *Trends Neurosci.*, **15,** 218-226, 1992.
4. H. Tiitinen, J. Sinkkonen, K. Reinikainen, K. Alho, J. Lavikainen and R. Näätänen, "Selective attention enhances the auditory 40-Hz transient response in humans", *Nature* **364,** 59-60, 1993.
5. C. Pantev, T. Elbert, S. Makeig, S. Hampson, C. Eulitz and M. Hoke, "Relationship of transient and steady-state auditory evoked fields", *Electroencephalogr. Clin. Neurophysiol.* **88,** 389-396, 1993.
6. P. May, H. Tiitinen, J. Sinkkonen and R. Näätänen, "Long-term stimulation attenuates the transient 40-Hz response", *Neuroreport* **5,** 1918-1920, 1994.
7. I.P. Jääskeläinen, J. Hirvonen, M. Saher, E. Pekkonen, P. Sillanaukee, R. Näätänen, and H. Tiitinen, "Benzodiazepine temazepam suppresses the transient auditory 40-Hz response amplitude in humans", *Neurosci. Lett.* **268,** 105-107, 1999.
8. J. Ahveninen, H. Tiitinen, J. Hirvonen, E. Pekkonen, J. Huttunen, S. Kaakkola and I.P. Jääskeläinen, "Scopolamine augments transient auditory 40-hz magnetic response in humans", *Neurosci. Lett.* **277,** 115-118, 1999.
9. A. Ahonen, M.Hämäläinen, M. Kajola, J. Knuutila, P. Laine, O. Lounasmaa, L. Parkkonen, J. Simola and C. Tesche, "122-channel SQUID instrument for investigating the magnetic signals from the human brain", *Physica Scripta*, **T49,** 198-205, 1993.
10. C.D. Tesche, M.A. Uusitalo, R.J. Ilmoniemi, M. Huotilainen, M. Kajola and O. Salonen, "Signal-space projections of MEG data characterize both distributed and well-localized

neuronal sources", *Electroencephalogr. Clin. Neurophysiol.* **95**, 189-200, 1995.

11. E.J. Bartlett, J.D. Brodie, P. Simkowitz, S.L. Dewey, H. Rusinek, A.P. Wolf, J.S. Fowler, N.D. Volkow, G. Smith, A. Wolkin and R. Cancro, "Effects of haloperidol challenge on regional cerebral glucose utilization in normal human subjects", *Am. J. Psychiatry* **151**, 681-686, 1994.
12. C. Tallon-Baudry, O. Bertrand and J. Pernier, "A ring-shaped distribution of dipoles as a source model of induced gamma-band activity", *Clin. Neurophysiol.* **110,** 660-665, 1999.
13. S.K. Goldsmith and J.N. Joyce, "Dopamine D_2 receptors are organized in bands in normal human temporal cortex", *Neuroscience* **74,** 435-451, 1996.